

CLAIMS

1. A variant Hepatitis B Virus (HBV) comprising a surface component exhibiting an altered immunological profile compared to a reference HBV.
2. A variant HBV according to claim 1 wherein the surface component on the variant is a surface antigen which comprises a single or multiple amino acid substitution, addition and/or deletion or truncation compared to a surface antigen from said reference HBV and wherein an antibody generated to the reference surface antigen from the reference HBV exhibits reduced capacity for neutralizing said variant HBV.
3. A variant HBV according to claim 2 wherein the surface antigen on the variant comprises an amino acid substitution, addition and/or deletion or truncation compared to the amino acid sequence set forth below:

$M X_1 X_2 X_3 X_4 S G X_5 L X_6 P L X_7 V L Q A X_8 X_9 F X_{10} L T X_{11} I X_{12} X_{13} I P$
 $X_{14} S L X_{15} S W W T S L N F L G X_{16} X_{17} X_{18} X_{19} C X_{20} G X_{21} N X_{22} Q S$
 $X_{23} X_{24} S X_{25} H X_{26} P X_{27} X_{28} C P P X_{29} C X_{30} G Y R W M C L X_{31} R F I I$
 $F L X_{32} I L L L C L I F L L V L L D X_{33} Q G M L X_{34} V C P L X_{35} P X_{36} X_{37}$
 $X_{38} T T S X_{39} X_{40} X_{41} C X_{42} T C X_{43} X_{44} X_{45} X_{46} Q G X_{47} S X_{48} X_{49} P X_{50} X_{51}$
 $C C X_{52} K P X_{53} X_{54} G N C T C I P I P S X_{55} W A X_{56} X_{57} X_{58} X_{59} L W E$
 $X_{60} X_{61} S X_{62} R X_{63} S W L X_{64} L L X_{65} X_{66} F V Q X_{67} X_{68} X_{69} X_{70} L X_{71} P X_{72} V$
 $W X_{73} X_{74} X_{75} I W X_{76} X_{77} W X_{78} W X_{79} P X_{80} X_{81} X_{82} X_{83} I X_{84} X_{85} P F X_{86}$
 $P L L P I F X_{87} X_{88} L X_{89} X_{90} X_{91} I [Formula I];$

wherein:

- X_1 is E or G or D;
 X_2 is N or S or K;
 X_3 is I or T;

[illegible]

- X_{31} is R or Q;
 X_{32} is F or C;
 X_{33} is Y or C;
 X_{34} is P or H or S;
 X_{35} is I or L;
 X_{36} is G or R;
 X_{37} is S or T;
 X_{38} is T or S;
 X_{39} is T or V or A;
 X_{40} is G or E or Q;
 X_{41} is P or A or S;
 X_{42} is K or R;
 X_{43} is T or M;
 X_{44} is T or I or S or A;
 X_{45} is P or T or A or I or L;
 X_{46} is A or V;
 X_{47} is N or T;
 X_{48} is M or K or L;
 X_{49} is F or Y or I;
 X_{50} is S or Y;
 X_{51} is C or S;
 X_{52} is T or I or S;
 X_{53} is T or S;
 X_{54} is D or A;
 X_{55} is S or T;
 X_{56} is F or L;
 X_{57} is A or G or V;

- X_{58} is K or R or T;
 X_{59} is Y or F;
 X_{60} is W or G;
 X_{61} is A or G;
 X_{62} is V or A;
 X_{63} is F or L;
 X_{64} is S or N;
 X_{65} is V or A;
 X_{66} is P or Q;
 X_{67} is W or C or S;
 X_{68} is F or C;
 X_{69} is V or D or A;
 X_{70} is G or E;
 X_{71} is S or F;
 X_{72} is T or I;
 X_{73} is L or P;
 X_{74} is S or L;
 X_{75} is A or V;
 X_{76} is M or I;
 X_{77} is M or I;
 X_{78} is Y or F;
 X_{79} is G or E;
 X_{80} is S or N or K;
 X_{81} is L or Q;
 X_{82} is Y or F or H or C;
 X_{83} is S or G or N or D or T;
 X_{84} is V or L;

- 40 -

X_{85} is S or N;
 X_{86} is I or M or L;
 X_{87} is F or C;
 X_{88} is C or Y;
 X_{89} is W or R;
 X_{90} is V or A; and
 X_{91} is Y or I or S;

and wherein the variant HBV is selected for by a nucleotide analogue of HBV DNA polymerase.

4. A variant HBV according to claim 2 wherein the surface antigen on the variant comprises an amino acid substitution, addition and/or deletion or truncation compared to the amino acid sequence setforth below:

$MX_1X_2X_3X_4SGX_5LX_6PLX_7VLQAX_8X_9FX_{10}LTX_{11}IX_{12}X_{13}IP$
 $X_{14}SLX_{15}SWWTS LNFLGX_{16}X_{17}X_{18}X_{19}CX_{20}GX_{21}NX_{22}QS$
 $X_{23}X_{24}SX_{25}HX_{26}PX_{27}X_{28}CPPX_{29}CX_{30}GYRWMCLX_{31}RFII$
 $FLX_{32}ILLCLIFLLVLLDX_{33}QGMLX_{34}VCPLX_{35}PX_{36}X_{37}$
 $X_{38}TTSX_{39}X_{40}X_{41}CX_{42}TCX_{43}X_{44}X_{45}X_{46}QGX_{47}SX_{48}X_{49}PX_{50}X_{51}$
 $CCX_{52}KPX_{53}X_{54}GNCTCIPISX_{55}WAX_{56}X_{57}X_{58}X_{59}LWE$
 $X_{60}X_{61}SX_{62}RX_{63}SWLX_{64}LLX_{65}X_{66}FVQX_{67}X_{68}X_{69}X_{70}LX_{71}PX_{72}V$
 W
 $X_{73}X_{74}X_{75}IW X_{76}X_{77}WX_{78}WX_{79}PX_{80}X_{81}X_{82}X_{83}IX_{84}X_{85}PFX_{86}PL$
 $LPIFX_{87}X_{88}LX_{89}X_{90}X_{91}I[\text{Formula I}];$

wherein:

- X_1 is E or G or D;
- X_2 is N or S or K;
- X_3 is I or T;
- X_4 is T or A;
- X_5 is F or L;
- X_6 is G or R;
- X_7 is L or R;
- X_8 is G or V;
- X_9 is F or C;
- X_{10} is L or S or W;
- X_{11} is R or K;
- X_{12} is L or R;
- X_{13} is T or K;
- X_{14} is Q or K;
- X_{15} is D or H;
- X_{16} is G or E or A;
- X_{17} is S or A or V or T or L;
- X_{18} is P or T;
- X_{19} is V or R or T or K or G;
- X_{20} is L or P;
- X_{21} is Q or L or K;
- X_{22} is S or L;
- X_{23} is P or Q;
- X_{24} is T or I;
- X_{25} is N or S;
- X_{26} is S or L;

- X_{27} is T or I;
 X_{28} is S or C;
 X_{29} is I or T;
 X_{30} is P or A;
 X_{31} is R or Q;
 X_{32} is F or C;
 X_{33} is Y or C;
 X_{34} is P or H or S;
 X_{35} is I or L;
 X_{36} is G or R;
 X_{37} is S or T;
 X_{38} is T or S;
 X_{39} is T or V or A;
 X_{40} is G or E or Q;
 X_{41} is P or A or S;
 X_{42} is K or R;
 X_{43} is T or M;
 X_{44} is T or I or S or A;
 X_{45} is P or T or A or I or L;
 X_{46} is A or V;
 X_{47} is N or T;
 X_{48} is M or K or L;
 X_{49} is F or Y or I;
 X_{50} is S or Y;
 X_{51} is C or S;
 X_{52} is T or I or S;
 X_{53} is T or S;

- X_{54} is D or A;
 X_{55} is S or T;
 X_{56} is F or L;
 X_{57} is A or G or V;
 X_{58} is K or R or T;
 X_{59} is Y or F;
 X_{60} is W or G;
 X_{61} is A or G;
 X_{62} is V or A;
 X_{63} is F or L;
 X_{64} is S or N;
 X_{65} is V or A;
 X_{66} is P or Q;
 X_{67} is W or C or S;
 X_{68} is F or C;
 X_{69} is V or D or A;
 X_{70} is G or E;
 X_{71} is S or F;
 X_{72} is T or I;
 X_{73} is L or P;
 X_{74} is S or L;
 X_{75} is A or V;
 X_{76} is M or I;
 X_{77} is M or I;
 X_{78} is Y or F;
 X_{79} is G or E;
 X_{80} is S or N or K;

- X_{81} is L or Q;
 X_{82} is Y or F or H or C;
 X_{83} is S or G or N or D or T;
 X_{84} is V or L;
 X_{85} is S or N;
 X_{86} is I or M or L;
 X_{87} is F or C;
 X_{88} is C or Y;
 X_{89} is W or R;
 X_{90} is V or A; and
 X_{91} is Y or I or S.

and wherein the variant HBV is selected for following immunological therapy directed against a surface antigen as defined in Formula I.

5. A variant HBV according to claim 1 comprising a nucleotide sequence having a single or multiple nucleotide substitution, addition and/or deletion or truncation of the nucleotide sequence as set forth in formula III below:

$ACN_1 AAACCTN_2 N_3 GGAN_4 GGAAAN_5 TGCACN_6 TGT$
 $ATTCCCATCCCATCN_7 TCN_8 TGGGCTTTTCGN_9 AA$
 $N_{10} ATN_{11} CCTATGGGAGN_{12} GGGCCTCAGN_{13} CCGT$
 $TTCTCN_{14} TGGCTCAGTTTACTAGTGCCATTTGT$
 $TCAGTGGTTTCGN_{15} AGGGGCTTTCCCCCACTGTN_{16}$
 $TGGCTTTTCAGN_{17} TATATGGATGATGTGGTN_{18} TT$
 $GGGGGCCAAGTCTGTACAN_{19} CATCN_{20} TGAGTCC$
 $CTTTN_{21} TN_{22} CCN_{23} CTN_{24} TTACCAATTTTCTTN_{25} TG$
 $TCTN_{26} TGGGN_{27} ATACATT$ [Formula III];

- 45 -

wherein:

- N_1 is A or C;
 N_2 is T or A;
 N_3 is C or T;
 N_4 is C or T;
 N_5 is C or T;
 N_6 is C or T;
 N_7 is A or G;
 N_8 is T or C;
 N_9 is C or G;
 N_{10} is G or A;
 N_{11} is T or A;
 N_{12} is T or G;
 N_{13} is T or C;
 N_{14} is C or T;
 N_{15} is T or C;
 N_{16} is T or C;
 N_{17} is T or C;
 N_{18} is A or T;
 N_{19} is A or G;
 N_{20} is T or G;
 N_{21} is A or T;
 N_{22} is A or G;
 N_{23} is T or G;
 N_{24} is A or G;
 N_{25} is T or C;
 N_{26} is T or C; and

N_{27} is T or C.

and wherein the HBV variant has a surface antigen exhibiting an altered immunological profile relative to the surface antigen as defined in Formula I.

6. An isolated variant Hepatitis B virus surface antigen (HBsAg) or a recombinant form thereof or a derivative or chemical equivalent thereof wherein said HBsAg or its recombinant or derivative form or its chemical equivalent exhibits an altered immunological profile compared to an HBsAg from a reference HBV.

7. An isolated variant HBsAg or a recombinant or derivative form thereof or a chemical equivalent thereof according to claim 6 wherein the variant HBsAg comprises an amino acid sequence having a single or multiple substitution, addition and/or deletion or truncation of the amino acid sequence set forth below:

$M X_1 X_2 X_3 X_4 S G X_5 L X_6 P L X_7 V L Q A X_8 X_9 F X_{10} L T X_{11} I X_{12} X_{13} I P$
 $X_{14} S L X_{15} S W W T S L N F L G X_{16} X_{17} X_{18} X_{19} C X_{20} G X_{21} N X_{22} Q S$
 $X_{23} X_{24} S X_{25} H X_{26} P X_{27} X_{28} C P P X_{29} C X_{30} G Y R W M C L X_{31} R F I I$
 $F L X_{32} I L L L C L I F L L V L L D X_{33} Q G M L X_{34} V C P L X_{35} P X_{36} X_{37}$
 $X_{38} T T S X_{39} X_{40} X_{41} C X_{42} T C X_{43} X_{44} X_{45} X_{46} Q G X_{47} S X_{48} X_{49} P X_{50} X_{51}$
 $C C X_{52} K P X_{53} X_{54} G N C T C I P I P S X_{55} W A X_{56} X_{57} X_{58} X_{59} L W E$
 $X_{60} X_{61} S X_{62} R X_{63} S W L X_{64} L L X_{65} X_{66} F V Q X_{67} X_{68} X_{69} X_{70} L X_{71} P X_{72} V$
 W
 $X_{73} X_{74} X_{75} I W X_{76} X_{77} W X_{78} W X_{79} P X_{80} X_{81} X_{82} X_{83} I X_{84} X_{85} P F X_{86} P L$
 $L P I F X_{87} X_{88} L X_{89} X_{90} X_{91} I [Formula I];$

wherein:

X_1 is E or G or D;

X_2 is N or S or K;

- X_3 is I or T;
 X_4 is T or A;
 X_5 is F or L;
 X_6 is G or R;
 X_7 is L or R;
 X_8 is G or V;
 X_9 is F or C;
 X_{10} is L or S or W;
 X_{11} is R or K;
 X_{12} is L or R;
 X_{13} is T or K;
 X_{14} is Q or K;
 X_{15} is D or H;
 X_{16} is G or E or A;
 X_{17} is S or A or V or T or L;
 X_{18} is P or T;
 X_{19} is V or R or T or K or G;
 X_{20} is L or P;
 X_{21} is Q or L or K;
 X_{22} is S or L;
 X_{23} is P or Q;
 X_{24} is T or I;
 X_{25} is N or S;
 X_{26} is S or L;
 X_{27} is T or I;
 X_{28} is S or C;
 X_{29} is I or T;

- X_{30} is P or A;
 X_{31} is R or Q;
 X_{32} is F or C;
 X_{33} is Y or C;
 X_{34} is P or H or S;
 X_{35} is I or L;
 X_{36} is G or R;
 X_{37} is S or T;
 X_{38} is T or S;
 X_{39} is T or V or A;
 X_{40} is G or E or Q;
 X_{41} is P or A or S;
 X_{42} is K or R;
 X_{43} is T or M;
 X_{44} is T or I or S or A;
 X_{45} is P or T or A or I or L;
 X_{46} is A or V;
 X_{47} is N or T;
 X_{48} is M or K or L;
 X_{49} is F or Y or I;
 X_{50} is S or Y;
 X_{51} is C or S;
 X_{52} is T or I or S;
 X_{53} is T or S;
 X_{54} is D or A;
 X_{55} is S or T;
 X_{56} is F or L;

- X_{57} is A or G or V;
 X_{58} is K or R or T;
 X_{59} is Y or F;
 X_{60} is W or G;
 X_{61} is A or G;
 X_{62} is V or A;
 X_{63} is F or L;
 X_{64} is S or N;
 X_{65} is V or A;
 X_{66} is P or Q;
 X_{67} is W or C or S;
 X_{68} is F or C;
 X_{69} is V or D or A;
 X_{70} is G or E;
 X_{71} is S or F;
 X_{72} is T or I;
 X_{73} is L or P;
 X_{74} is S or L;
 X_{75} is A or V;
 X_{76} is M or I;
 X_{77} is M or I;
 X_{78} is Y or F;
 X_{79} is G or E;
 X_{80} is S or N or K;
 X_{81} is L or Q;
 X_{82} is Y or F or H or C;
 X_{83} is S or G or N or D or T;

- 50 -

X_{84} is V or L;
 X_{85} is S or N;
 X_{86} is I or M or L;
 X_{87} is F or C;
 X_{88} is C or Y;
 X_{89} is W or R;
 X_{90} is V or A; and
 X_{91} is Y or I or S;

and wherein a neutralizing antibody directed to a reference HBV exhibits no or reduced neutralizing activity to an HBV carrying said variant HBsAg.

8. An isolated variant HBsAg according to claim 7 encoded by a nucleotide sequence having a single or multiple nucleotide substitution, addition and/or deletion or truncation relative to the nucleotide sequence set forth below:

ACN₁AAACCTN₂N₃GGAN₄GGAAAN₅TGCACN₆TGTA
 TTCCCATCCCATCN₇TCN₈TGGGCTTTTCGN₉AAN₁₀A
 TN₁₁CCTATGGGAGN₁₂GGGCCTCAGN₁₃CCGTTTCTC
 N₁₄TGGCTCAGTTTACTAGTGCCATTTGTTTCAGTGG
 TTCGN₁₅AGGGCTTTCCCCCACTGTN₁₆TGGCTTTCA
 GN₁₇TATATGGATGATGTGGTN₁₈TTGGGGGGCCAAG
 TCTGTACAN₁₉CATCN₂₀TGAGTCCCTTTN₂₁TN₂₂CCN₂₃
 CTN₂₄TTACCAATTTTCTTN₂₅TGTCTN₂₆TGGGN₂₇ATA
 CATT [FORMULA III];

wherein:

N₁ is A or C;

[illegible]

- 52 -

9. A variant HBV or an isolated HBsAg from said variant HBV wherein said variant HBV comprises an HBsAg having a single or multiple amino acid substitution, addition and/or deletion or truncation relative to the HBsAg on a reference HBV and whereas the HBsAg variant is defined by a single or multiple amino acid substitution, addition and/or truncation to the catalytic region of HBV DNA polymerase as defined below:

SZ₁LSWLSLDVSAAFYHZ₂PLHPAAMPHELLZ₃GSS
 GLZ₄RYVARLSSSZ₅SZ₆Z₇XNZ₈QZ₉Z₁₀XXXZ₁₁LHZ₁₂Z₁₃
 CSRZ₁₄LYVSLZ₁₅LLYZ₁₆TZ₁₇GZ₁₈KLHLZ₁₉Z₂₀HPIZ₂₁L
 GFRKZ₂₂PMGZ₂₃GLSPFLLAQFTSAIZ₂₄Z₂₅Z₂₆Z₂₇Z₂₈R
 AFZ₂₉HCZ₃₀Z₃₁FZ₃₂YM'DDZ₃₃VLGAZ₃₄Z₃₅Z₃₆Z₃₇HZ₃₈EZ₃₉
 LZ₄₀Z₄₁Z₄₂Z₄₃Z₄₄Z₄₅Z₄₆LLZ₄₇Z₄₈GIHLNPZ₄₉KTKRWGYS
 LNFMGYZ₅₀IG [Formula II];

wherein:

- X is any amino acid;
- Z₁ is N or D;
- Z₂ is I or P;
- Z₃ is I or V;
- Z₄ is S or D;
- Z₅ is T or N;
- Z₆ is R or N;
- Z₇ is N or I;
- Z₈ is N or Y or H;
- Z₉ is H or Y;
- Z₁₀ is G or R;
- Z₁₁ is D or N;
- Z₁₂ is D or N;

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- Z_{13} is S or Y;
 Z_{14} is N or Q;
 Z_{15} is L or M;
 Z_{16} is K or Q;
 Z_{17} is Y or F;
 Z_{18} is R or W;
 Z_{19} is Y or L;
 Z_{20} is S or A;
 Z_{21} is I or V;
 Z_{22} is I or L;
 Z_{23} is V or G;
 Z_{24} is C or L;
 Z_{25} is A or S;
 Z_{26} is V or M;
 Z_{27} is V or T;
 Z_{28} is R or C;
 Z_{29} is F or P;
 Z_{30} is L or V;
 Z_{31} is A or V;
 Z_{32} is S or A;
 Z_{33} is V or L or M;
 Z_{34} is K or R;
 Z_{35} is S or T;
 Z_{36} is V or G;
 Z_{37} is Q or E;
 Z_{38} is L or S or R;
 Z_{39} is S or F;

- 54 -

Z₄₀ is F or Y;
Z₄₁ is T or A;
Z₄₂ is A or S;
Z₄₃ is V or I;
Z₄₄ is T or C;
Z₄₅ is N or S;
Z₄₆ is F or V;
Z₄₇ is S or D;
Z₄₈ is L or V;
Z₄₉ is N or Q;
Z₅₀ is V or I; and
M* is amino acid 550.

10. A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of G112R, T123P, Y/F134S, D144E, G145R, A157D, E164D, F170L, M195I, W196L, S196W, W196STOP, M198I, W199S, S204T and S210R wherein "STOP" means a stop codon.

11. A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of :
D144E, G145R, A157D, E164D, M195I, W196L, S196W, W196STOP, M198I, W199S and S210R wherein "STOP" means a codon.

12. A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of:
Q476, N480G, N485K, K495R, R499O, G499E, W499Q, F512L, I515L, V519L, L526M, M550V, M550I, V553I and S565P.

13. A composition comprising a variant HBV or variant HBsAg according to any one of

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- 55 -

SUB A1 could

claims 1 to 12 or a ~~recombinant~~ or derivative form or its chemical equivalent.

14. A composition according to claim 13 further comprising one or more pharmaceutically acceptable carriers and/or diluents.

SUB A2

15. A method for the treatment or prophylaxis of HBV infection said ~~method~~ comprising administering to a subject an amount of a variant HBV or variant HBsAg according to any one of claims 1 to 12 or a composition according to claim 13 or 14, said amount being effective to induce an immune response to said variant HBV.

16. Use of a variant HBV or an HBsAg from said HBV in the manufacture of a medicament for the treatment or prophylaxis of infection by said variant HBV.

17. Use of a variant HBV or an HBsAg from said variant HBV in screening for an agent useful in the treatment or prophylaxis of infection by said variant HBV.

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